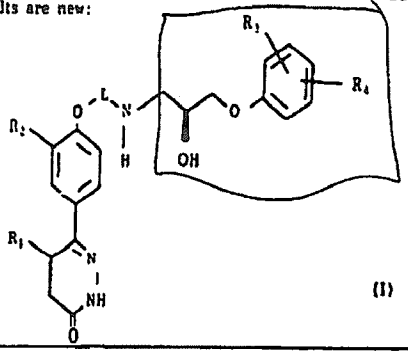
91-045935/07 B03 GLAX 10.08.89
GLAXO INC *EP -412-814-A
01.09.89-US-402179 (+US-392233) (13.02.91) A61k-31/50
C07d-237/04

New pyridazinone derivs. - have beta blocking activity for treatment of congestive heart failure

C91-019457 R(AT BE CH DE DK ES FR GB GR IT LI LU NL SE)

B(7-D10, 12-E2, 12-E6B, 12-F1B)

Pyridazinone derivs. of formula (I) and their acid addn salts are new:



(I)

R_1 = H or lower alkyl;
R_2 = H, halo, CF_3, CN, lower alkyl or lower alkoxy;
L = $(CR_5R_6)_nCON(R_7)CR_8R_9CR_{10}R_{11}$ (gp. (a)) or $(CR_5R_6)_p$ (gp. (b));
R_5 - R_{11} = H or lower alkyl;
n = 1-3;
p = 2-6;
R_3, R_4 = H, alkoxy, morpholino, CN, halo, CF_3, alkyl, alkylsulphonyl, alkoxyalkyl, cycloalkylalkoxyalkyl, NO_2, OH, alkenyloxy, NH_2 or mono- or di-alkylamino.

MORE SPECIFICALLY
R_1 = H or Me;
R_2 = H or Cl;
L = (a);
n = 1 or 3;
R_5 - R_9 = H;
R_{10}, R_{11} = H or Me;
R_3 = H;
R_4 = CN, Cl or Me.

USE

(I) are useful for treating congestive heart failure. In tests (I) exhibit inotropic and β-adrenergic blocking activity Dose is 0.1-5 mg/kg 1-4 times a day.

SPECIFICALLY CLAIMED

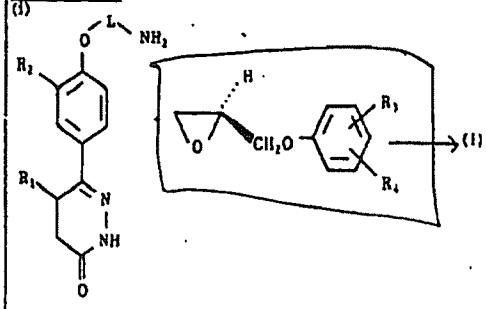
4 Cpds. (I) e.g.
6-(4-(N-(2-(2-cyanophenoxy)-2-hydroxypropylamino)-2-methylpropyl)carbamoylmethoxy-3-chlorophenyl))-4,5-dihydro-3(2H)-pyridazinone; and
6-(4-(N-(2-(3-(2-cyanophenoxy)-(2S)-hydroxypropylamino) ethyl)carbamoylpropoxy-3-chlorophenyl))-4,5-dihydro-3(2H)-pyridazinone.

WIDER DISCLOSURE

Intermediates of formula (VI) (see 'Starting Matrials') and (VII) (see 'Preparation') are new.

PREPARATION

(i)



(VII)

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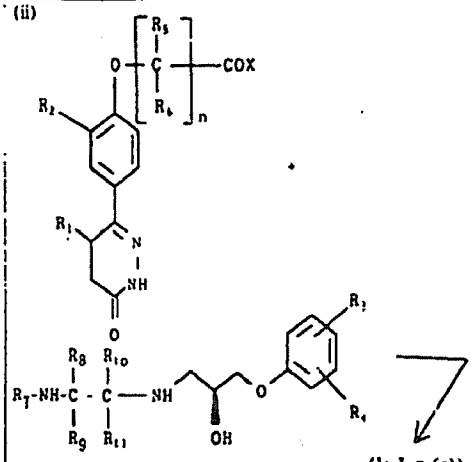
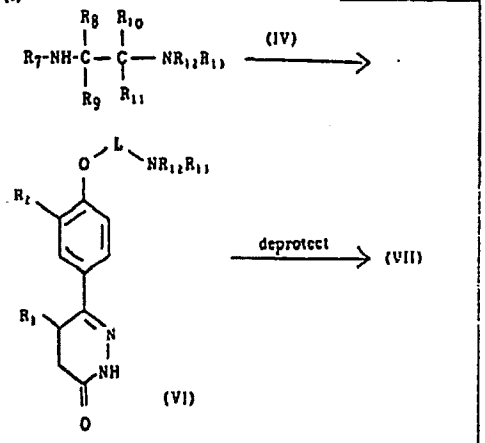
(ii)



(I; L = (a))

STARTING MATERIALS

(i)



(VI)

(con't)

R_{12} = H;
R_{11} = amino protecting gp.;
or R_{12} + R_{11} = divalent amino protecting gp.

EXAMPLE

A soln. of 499 mg 6-[4-(2-aminoethylcarbamoyl-methoxy)phenyl]-5-methyl-4,5-dihydro-3(2H)-pyridazinone and 208 ml (2S)-(+)-3-phenoxy-1,2-epoxypropane in 10 ml MeCN is refluxed for 10 hr. then evapd. The residue is taken up in $CHCl_3$/MeOH (1:1) (10ml) then flash chromatographed over silica gel eluting with $CHCl_3$/MeOH (90:10) (500 ml) then $CHCl_3$/MeOH/NH_4OH (90:10:2) (1 l) to give 423 mg (50%) 6-[4-[N-(2-(3-phenoxy-2-hydroxy-propylamino)ethyl)carbamoylmethoxyphenyl]-5-methyl-4,5-dihydro-3(2H)-pyridazinone (Ia).

This is dissolved in 15 ml EtOAc. 5 ml ether are added. 12 ml 0.1 N Maleic acid in ether are added with stirring. The ppte. is filtered, washed with ether and dried overnight at 50°C in vacuo to give (Ia) maleate, m.pt. 58-73°C (59pp985EDDwgNo0/0).

(E) ISR: No Search Report.